REMARKS

Claims 101, 102, 104-106, 109-116 and 120-127 are pending in the present application.

THE DOUBLE PATENTING REJECTION

Applicants hereby request that any double-patenting rejection continue to be held in abeyance until the present claims are indicated to be allowable but for the double-patenting rejection, at which time Applicants intend to submit a Terminal Disclaimer, thereby obviating the rejection.

REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claims 101, 102, 104-106, 109-116 and 120-127 under 35 U.S.C. 103 as being obvious over Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*. Applicants respectfully traverse this rejection.

Initially, the Applicants kindly direct the Examiner's attention to MPEP paragraph 707.07(j)(III), "State When Claims are Allowable." The Applicants respectfully assert that the Examiner has previously indicated that claim 101 is allowable (Office Action, Dec. 31, 2003, para. 6 and 7). Therefore, Applicants respectfully assert that claim 101 and any claims dependant therefrom are allowable and request further action commensurate therewith.

Additionally, the Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness. As discussed in MPEP 2143,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present Office Action, the Examiner recites that:

"Abe *et al* teaches an AH6 antibody that is specific for a Lewis Y carbohydrate antigen of which that has been complexed with a secondary antibody (see page 2639, 2nd col.). Abe *et al* indicate that this antibody-second antibody complex was able to localize the antibody to specific regions of a tumor tissue (see figure 2, page 2641). This "immunoconjugate" has thus been proven to be useful for the localization and detection of an antigen on a tumor cell."

1. **There is no suggestion or motivation to modify or combine Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al***

The Applicants respectfully assert that Abe *et al* do not teach or suggest an "immunoconjugate that comprises an antibody joined to a therapeutic agent" as claimed in claim 101. The Examiner previously admitted that "Abe *et al* do not specifically characterize the antibody as being in the form of an immunoconjugate." (Office Action, August 25, 2004, page 3, lines 18-19). A biotinylated secondary antibody which binds to a primary antibody, AH6, in an immunohistological assay for labeling formalin-fixed tissues samples is not "an immunoconjugate that comprises an antibody joined to a therapeutic agent." For example, many home pregnancy tests utilize a monoclonal antibody specific to hCG conjugated to a dye to detect its presence in urine. However, the treatment of pregnancy is not the home pregnancy test. For example, treatment may include, in an uncomplicated pregnancy, diet, vitamins, and regular obstetrician visits.

The application describes an immunoconjugate as "... any molecule or ligand such as an antibody or growth factor chemically or biologically linked to a cytotoxin, a radioactive agent, an anti-tumor drug or *a therapeutic agent*." (page 27, lines 1-4 of application). (emphasis added). The application describes a therapeutic agent as "... any agent useful for *therapy* including anti-tumor drugs, cytotoxins, cytotoxin agents, and radioactive agents." (page 28, lines 1-3 of the application). (emphasis added). The application distinguishes "therapy" from diagnosis at least on page 5, line 5 ("therapy *or* diagnosis"). (emphasis added). Abe *et al* discuss the use of a Vecstatin ABC Kit ("**Immunohistological Examination of Tissue Sections**", column 2, lines 34-37.) The use of avidin-biotin interaction in immunoenzymatic techniques provides a method to localize antigens in formalin-fixed tissues. Abe *et al* describe the use of the Vecstatin ABC Kit for localizing markers on prepared tissue sections by exposing the tissue section to a primary antibody, AH6, which is capable of specifically binding the marker of

interest; exposing the tissue section to a biotinylated antibody raised against the primary antibody; exposing the tissue section to a preformed labeling complex formed by reacting avidin and a biotinylated macromolecules, localizing the marker by reacting the detectable enzyme with substrate and observing the reaction. Thus, a label may be attached to the desired antigen site on the cell. To the best of the Applicant's understanding, the Examiner is comparing the biotinylated antibody to the "therapeutic agent." However, the biotinylated antibody is part of the immunohistological assay. It is not a "therapeutic agent", i.e., "an agent useful for therapy." Applicants assert that (1) Abe *et al* is merely describing a method to localize antigens in formalin-fixed tissues using a secondary antibody; (2) the "complex" in Abe *et al* does not include "a therapeutic agent"; and (3) the "complex" in Abe *et al* is not an "immunoconjugate." Therefore, the applicants respectfully assert that the antibody-secondary antibody complex in the immunohistological assay described by Abe *et al* is not "an immunoconjugate".

There is no suggestion or motivation, either in Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al* or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references. Abe *et al* fail to teach or suggest, as recited in claim 101, "[a]n immunoconjugate that comprises an antibody joined to a therapeutic agent...".

Oldham *et al* fail to satisfy the deficiencies of Abe *et al*. Oldham *et al* do not teach or suggest "...an immunoglobulin or antigen-binding fragment thereof that competitively inhibits binding of the monoclonal antibody BR96...". The Examiner recites that "Oldham et al taught that antibodies to tumor specific antigens "can be conjugated with a variety of toxic agents and administered either in vivo or used in vitro for therapeutic effect"." Rather than "...an immunoglobulin ... that competitively inhibits binding of the monoclonal antibody BR96...", Oldham *et al* describes the administration of an immunoconjugate of D3 diphtheria-toxin A chain for the attempted treatment of hepatonoma. Rather than as suggested by the Examiner immediately above, Oldham *et al* recite that techniques to conjugate an antibody to a variety of toxic

substances are difficult and require further refinement. Oldham *et al*, page 22, lines 25-27.

Sahagan *et al* do not satisfy the deficiencies of either Oldham *et al* or Abe *et al*. Sahagan *et al* do not even discuss immunoconjugates, let alone their therapeutic use.

2. There is no reasonable expectation of success in the combination of Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*

There is no reasonable expectation of success in the combination of Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*. The Examiner recites that "one of skill in the art would have found sufficient motivation and a reasonable expectation of success because Abe *et al* taught a tumor targeting antibody as well as an immunoconjugate, Oldham *et al* taught that any antibody so long as it targets a tumor specific antigen can be conjugated to a toxic agent and further showed effectiveness of an antibody conjugated to a toxin reduced tumor burden." The Applicants must respectfully disagree. First, as discussed above, Abe *et al* did not disclose an immunoconjugate, but merely the components of an immunohistological assay. Second, also as mentioned above, Oldham *et al* recite that techniques to conjugate an antibody to a variety of toxic substances are difficult and require further refinement. Finally, the studies conducted by Oldham *et al* did not show effectiveness but reported that the treated animals "did *manifest tumor growth* and subsequently *died from progressive tumor growth*." (emphasis added) Oldham *et al*, Page 20, lines 19-22.

The development of an immunoconjugate is not obvious. *In vitro*, the activity of immunoconjugates is affected by the number of target antigens on the cell surface, the internalization of the immunoconjugates, the kind of toxin, the class of the antibody, the kind of linkage, and by other factors. Dillman, *Annals of Internal Medicine* 111:592-603,595,596 *(1989)*.[1] Several problems arise with *in vivo* administration of immunoconjugates. The short serum half-life of immunoconjugates, due to their rapid hepatic uptake, decreases the number of immunoconjugate molecules that reach a solid tumor. This, together with low tumor penetration by immunoconjugates, could lead to low anti-tumor activity. Heterogeneity of tumors, immunogenicity of immunoconjugates,

sometimes marked differences in the biodistribution of antibody-drug conjugates from those seen with free antibody, the shedding of tumor antigens into the circulation, and cross-reactivity of immunoconjugates with normal tissues are other factors that might limit the clinical use of immunoconjugates. Further, in order for an immunoconjugate to be effective, the antibody with the immunoconjugate must be internalized and the cytostatic or cytotoxic component of the immunoconjugate cleaved and released in an active form within the cell. Dillman, pg 595, 596. Therefore, it cannot be presumed that any immunoconjugate will have a reasonable expectation of success.

Oldham *et al* do not satisfy the deficiencies of Abe *et al*. As recited above, Oldham *et al* discuss an experiment using an immunoconjugate that resulted in tumor growth and subsequently death of the test animals from progressive tumor growth. Oldham et al, Page 20, lines 19-22. Oldham *et al* is not indicative of a "reasonable expectation of success" of an immunoconjugate.

Also as mentioned above, Sahagan *et al* do not satisfy the deficiencies of either Oldham *et al* or Abe *et al*. Sahagan *et al* do not even discuss immunoconjugates, let alone their therapeutic use. The Examiner recites that Sahagan *et al* teach the construction of a chimeric antibody comprising a mouse variable region and a human constant region, wherein the purpose of such a construction is to reduce the side effects associated with mouse constant regions in eliciting an unwanted immune response. However, Applicants respectfully assert that the addition of a human Fc region onto a mouse antibody may not circumvent the immune response. See, Baert *et al* N Engl J. Med 348 (7):601-8 (2003); Welt *et al* Clin Cancer Res 9:1338-1346 (2003). The Applicants respectfully assert that it would not have been obvious to construct "[a]n immunoconjugate that comprises an antibody" wherein "the antibody comprises a human Fc region" as claimed in claim 101 and any claims dependant therefrom.

3. The references do not teach or suggest all the elements of the claims

Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al* fail to teach or suggest "an immunoconjugate that comprises an antibody joined to a therapeutic agent" as claimed in claim 101. Abe *et al* does not teach or suggest an

[1] Cited by Applicants as DI3 in Information Disclosure Statement dated August 9, 2000.

immunoconjugate. While mentioning immunoconjugates, Oldham *et al* disclose techniques to conjugate an antibody to a variety of toxic substances are difficult and require further refinement. Sahagan *et al* do not discuss immunoconjugates. Therefore, the references do not teach or suggest, as recited in claim 101, "an immunoconjugate that comprises an antibody joined to a therapeutic agent." As such, claim 101 and any claims dependant therefrom, are unobvious over Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Claims 101, 102, 104-106, 109-116 and 120-127 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call the undersigned attorney at (425)527-4122 if any questions or issues remain.

Respectfully submitted,

Date May 9, 2005 Vita G. Conforti 39,639 (Reg. No.)

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